

### **REMARKS/ARGUMENTS**

Upon entry of this amendment, claim 1 will be amended. Claims 1-11, 13, 14 and 16 remain pending, with claims 1 and 10 being independent claims.

By the amendment herein, claim 1 has been amended to even further clarify its subject matter as discussed in the response to 35 U.S.C. 112, second paragraph, below.

Applicants note that the Listing of Claims includes the identifier for claim 10 of “Previously Presented”, because the claim was amended in the Amendment filed March 19, 2007 to remove “or a solvate thereof or a hydrate thereof”.

Reconsideration and allowance of the application are respectfully requested.

#### **Discussion Of Interview**

Applicants express appreciation for the courtesies extended by the Examiner to Applicants’ representative Arnold Turk during a December 6, 2007 telephone interview at the Patent and Trademark Office.

During the interview, the indefiniteness rejection under 35 U.S.C. 112, second paragraph, was discussed. In particular, amendment of claim 1 to delete “or X<sup>1</sup>” language and arguments regarding the remaining rejections were discussed. The Examiner indicated that the arguments appeared to be acceptable, and that the arguments should be submitted in writing for further review.

Regarding the 35 U.S.C. 103(a) and obviousness-type double patenting rejections, differences between the documents utilized in the rejections and Applicants’ claims were discussed, and the Examiner was reminded regarding the previously filed Declaration Under 37

C.F.R. 1.132, filed March 19, 2007. The Examiner indicated that he would reconsider the record including Applicants' previously filed Declaration.

The Examiner indicated that a patentability conference would be conducted upon presentation of arguments in writing, and that the Examiner would contact Applicants if additional information was needed with respect to allowance of the application.

**Rejection Under 35 U.S.C. 112, second paragraph**

In response to the rejection of claims 1-9, 11, 13, 14 and 16 under 35 U.S.C. 112, second paragraph, Applicants respectfully submit the following.

Applicants note that claim 1 has been amended to delete "or X<sup>1</sup>" language to even further clarify the claimed subject matter. Therefore, the rejection based upon the assertion that "when ring represented by X or X<sup>1</sup>" in the claims renders the claims indefinite should be withdrawn.

Regarding the remaining grounds set forth in this rejection, Applicants respectfully submit that the scope of Applicants' claims are readily understandable so that one having ordinary skill in the art would understand the scope and content of the claimed subject matter so that the rejection should be withdrawn.

The rejection contends that the recitation of "m=1 to 3" and "n=0-8" in claim 1 renders claim 1 and the dependent claims indefinite as the maximum number of substituents is exceeded if as many of 11 substituents are included.

In response, Applicants submit that one having ordinary skill in the art would readily understand the scope and content of the claims, and would understand that substituents included in Applicants' claims include up to the maximum number of substituents permitted. Applicants submit that one having ordinary skill reading the claimed subject matter would understand that the

maximum amount of substituents is controlled by the maximum permitted individual substitutions for each of m and n. For example, if 8 substituents are permitted, one having ordinary skill in the art would understand that up to three of the substituents can be associated with m and the remainder can be associated with n.

Accordingly, this ground of rejection should be withdrawn.

With regard to claim 2, the rejection contends that claim 2 and dependent claims 3-9 are indefinite because  $Z=N$  with  $q=0$  would leave N with one valence requirement not met or met with an undefined group.

In response, Applicants submit that one having ordinary skill in the art would readily understand the scope and content of the claims, whereby this ground of rejection should be withdrawn. As illustrated in formula (II), substituent Y can be at any location on the ring and can therefore be a substituent associated with Z. Thus, the one valence requirement of N as questioned in the rejection can be met by substituent Y.

Accordingly, this ground of should be withdrawn.

As discussed with the Examiner during the above-noted interview, Applicants submit that the claims as presently written definitely recite Applicants' claimed subject matter. However, if the Examiner deems that any amendments would be beneficial to the claims to even more clearly define Applicants' claimed subject matter, the Examiner is requested to contact the undersigned to discuss the same.

### **Response To Art-Based Rejection**

Claims 1-5, 8, 9 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/70728 (hereinafter "WO '728") to Almario-Garcia et al. in view of EP 1136482 (hereinafter "EP '482") to Almario-Garcia et al., with the rejection contending that U.S. Patent No. 6,844,335 is equivalent.

Initially, prior to discussing the merits of the rejection, Applicants note that the rejection improperly includes canceled claims 12 and 15.

Regarding the merits of the rejection, Applicants note that the rejection states that WO '728 is different from Applicants' claims in exemplifying compounds wherein the nitrogen of the pyrimidine ring has hydrogen instead of alkyl as recited in Applicants' claims. Moreover, the rejection states that EP '482 is different from Applicants' claims in not exemplifying compounds wherein ring formed with R<sup>1</sup> and R<sup>2</sup> taken together have substituents. The rejection further contends that WO '728 teaches all of the elements of the instant claims except the instant R choice, while EP '481 teaches such R choices. The rejection concludes that one trained in the art would be motivated to combine the teachings of the primary reference and the second reference and expect the resultant compound to have the same use as disclosed in the references in view of combined equivalency teachings of active compounds with H and alkyl substituents on second nitrogen of the pyrimidone.

Regarding this ground of rejection, the Examiner is reminded that a rejection based upon EP '482 was previously withdrawn in view of Applicants' arguments and a Declaration Under 37 C.F.R. 1.132, filed March 19, 2007. In particular, Applicants submitted that one having ordinary skill in the art would not have been motivated to arrive at Applicants' claimed subject matter from the disclosure of EP '482, and that the compounds of the present invention have more potent TPK1

inhibitory activity compared to that of the compounds disclosed in EP '482. As is disclosed at page 15, lines 53 and 54 of EP '482, GSK3 $\beta$  (=TPK1) inhibitory activities of the compounds disclosed in EP '482, which are expressed in IC<sub>50</sub> values, are between 0.1 to 10 micromolar concentrations (= 100 to 10,000 nM).

In the Declaration Under 37 C.F.R. 1.132 by one of the inventors, Dr. Kazutoshi Watanabe, experiments are provided showing the inhibitory activity of Compounds 38 and 39 of EP '482, as compared to compounds of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1. In this regard, Applicants again note that it appears that Compound Nos. 38 and 39 of EP '482 appear to be the closest compounds to Applicants' claimed subject matter. In fact, the present rejection appears to be agreeing that Compound Nos. 38 and 39 of EP '482 are the closest to the compounds recited by Applicants by referencing these compounds in the present rejection. Also, the Examiner is reminded that during an August 2, 2007 interview (as discussed in the Amendment Under 37 C.F.R. 1.116, filed September 4, 2007), the Examiner indicated that the evidence produced in Applicants' Declaration was sufficient to overcome the teachings of EP '482 in view of the superior results shown therein, and therefore he previously withdrew the rejection based upon EP '482.

Therefore, the Examiner is once again referred to the Declaration referring to Compound Nos. 38 and 39 of EP '482 and the Table attached to the Declaration for comparison of the compounds according to the present invention as compared to comparative compounds of EP '482 which are revealed to have much lower inhibitory activity. As shown in the Declaration, Compound Nos. 38 and 39 of EP '482 have IC<sub>50</sub> values of >1000 nM. In contrast, compounds according to the present invention have TPK1 inhibitory activities between 0.25 to 43 nM. Applicants submit that these results are unexpected by one of ordinary skill in the art.

Still further, TPK1 inhibitory activities expressed in IC 50 of the compounds disclosed in WO '728 are between 0.1 to 10 micromolar concentrations (100 to 10,000 nM) as shown at page 26 of WO '728. The activities are therefore far weaker than those of the compounds of Applicants' claims.

Accordingly, Applicants submit that one having ordinary skill in the art would not have combined the disclosures of WO '728 and EP '482. However, even if for the sake of argument the disclosures were combined, Applicants' claimed subject matter includes unexpected results which are not taught or suggested by the documents utilized in the rejection, so that the rejection of record should be withdrawn.

#### **Response To Obviousness-Type Double Patenting Rejections**

The following obviousness-type double patenting rejections are set forth in the Office Action.

(a) Claims 1-11, 13, 14 and 16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,844,335 in view of WO 01/70728,

(b) Claims 1-11, 13, 14 and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7, 16-24, 31-39 and 41-45 of copending Application No. 11/035,264.

In response and so that the record is complete, Applicants' initially note that U.S. Patent No. 6,884,335 is indicated to be a National Stage of PCT /EP01/03640, which published as WO 01/70729 on September 27, 2001, which is more than one year prior to the filing of the present International Application on March 26, 2004. Still further, the rejection above indicates that U.S. Patent No. 6,844,335 is an equivalent of EP '482.

Still further, Applicants note that Application No. 11/035,264 is a divisional application based upon Patent No. 6,884,335.

Initially, Applicants note that the rejection over the '335 patent is unclear, because the statement of the rejection refers to claim 1 of the '335 patent; whereas, the body of the rejection once again refers to claims 1-50 of the '335 patent. Therefore, clarification of this ground of rejection is once again requested.

Regarding the merits of the rejections, Applicants note that the Examiner has indicated at the above-noted interview that the evidence presented in Applicants' Declaration was sufficient to overcome the teachings of EP '482 in view of the superior results shown therein. Therefore, as noted above, the Examiner has indicated that he has withdrawn the rejection based upon EP '482 in view of the unexpected showings in the Declaration. During the above-noted interview, the Examiner again acknowledged that he believed that the evidence presented in Applicants' Declaration was sufficient to overcome the teachings of EP '482 in view of the superior results shown therein.

Therefore, as each of the present rejections relies upon claims of a patent/application that at most includes subject matter disclosed by EP '482 (as the Examiner has noted that U.S. Patent No. 6,844,335 is an equivalent of EP '482), the obviousness-type double patenting rejections should be withdrawn at least for the reasons advance above with respect to the rejection including EP '482. Initially, Applicants note that this application is a divisional application of the U.S. 6,844,335 utilize in the rejection discuss above.

Therefore, these grounds of rejection should be withdrawn.


### CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
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